Safety of Carbamazepine Extended-Release Capsules Used in Combination with Other Psychotropic Medications for the Treatment of Bipolar I Disorder

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ABSTRACT

Objective: To evaluate the safety and efficacy of carbamazepine extended-release capsules (CBZ-ERC) in combination with other psychotropic medications for the treatment of bipolar I disorder.

Design: In this Phase IIIb, open-label, eight-week, observational, polypharmacy study, adult subjects were started on CBZ-ERC 200mg and titrated over four weeks to optimal dose (1600mg/d maximum). Concomitant lithium and atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole) were permitted. Safety assessments included adverse events, laboratory parameters, physical examination, medication history, vital signs, and electrocardiogram. Efficacy measures included the Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), and Clinical Global Impressions Scale–Bipolar Version (CGI-BP). All data were summarized using descriptive statistics.

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Results: Overall, 45 (84.9%) subjects reported treatment-emergent adverse events (TEAEs); most were mild or moderate in severity. The most commonly reported TEAEs were somnolence (n=14, 26.4%), sedation (n=12, 22.6%), dizziness (n=11, 20.8%), headache (n=9, 17.0%), and nausea (n=7, 13.2%). There were no clinically significant changes in vital signs, including weight. Mean changes in laboratory parameters were small, with values that were within the normal range for the majority of subjects. Few changes relative to screening for other safety parameters occurred. Mean total YMRS score decreased from baseline at each study visit. HAM-D and MADRS scores decreased from baseline at Weeks 4 and 8, and all three CGI-BP components (overall bipolar disorder, mania, and depression) improved during the study.

Conclusion: CBZ-ERC appears to be safe and effective for use in combination with atypical antipsychotics and lithium for treatment of bipolar I disorder.

INTRODUCTION

Current options for the treatment of bipolar disorder include the Food and Drug Administration (FDA)-approved mood stabilizers (e.g., lithium, valproate, lamotrigine, and carbamazepine extended-release capsules [CBZ-ERC]) and antipsychotics (e.g., chlorpromazine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole). While these agents have been shown in double-blind trials to be effective for the management of acute mania,[1–11] bipolar disorder is a lifelong disorder with frequently recurring symptoms.[12] It has been estimated that 37 percent of patients who have a manic episode suffer a recurrence within one year, and 73 percent experience a recurrence within five years.[13] Further, a long-term follow-up estimate of the lifetime outcome of bipolar disorder determined that only 16 percent of patients had recovered with treatment, while recurrence was observed in 52 percent of patients.[14]

It has long been recognized that long-term treatment of bipolar disorder with monotherapy is not always the most successful approach;[15] therefore, switching therapies or combining therapies is often used to manage bipolar episodes.[16–18] Several recent studies suggest that greater therapeutic benefit is achieved with combination therapy compared with monotherapy,[19–23] and recent studies have reported that, while 18 percent of patients with bipolar disorder receive monotherapy,[24] approximately 30 to 50 percent are treated with three or more agents concurrently.[18,24,25]

In general, polypharmacy is recognized as potentially placing patients at increased risk for adverse events (AEs), as well as creating the potential for drug-drug interactions.[26,27] However, although there is an increased potential for drug-drug interactions with concomitant therapies, polypharmacy also can, at times, decrease the incidence of AEs when the dosage of each drug in the combination regimen is lower than that of the monotherapy regimen.[28] In addition, the total cost of medications is higher with polypharmacy; nevertheless, by improving medical outcomes when appropriately prescribed, polypharmacy has been shown, in the management of other chronic medical conditions, to decrease the overall cost of healthcare.[29,30] The adverse event burden may be less for some patients with combination therapy, because lower doses can often be used to obtain the same effect. The improved efficacy of carbamazepine in combination with lithium compared with the use of either agent alone in bipolar disorder—especially in patients with a history of rapid cycling—has been demonstrated in a double-blind study.[31] The safety of CBZ-ERC in combination with commonly used mood stabilizers and antipsychotic agents was demonstrated in a recent clinical trial.[32] The purpose of this open-label study is to explore further the safety and efficacy of CBZ-ERC in combination with other psychotropic medications in the treatment of bipolar I disorder.

METHODS

This Phase IIIb, open-label, observational, polypharmacy study was conducted in accordance with current applicable regulations, the International Conference on Harmonisation (ICH), and local ethical and legal requirements. Before site initiation, protocols, informed consent documents, and relevant supporting and patient recruitment information were submitted to and reviewed and approved by a centralized Institutional Review Board (IRB), BioMed IRB. All subjects provided informed consent before they completed any study-related procedures.

Subjects. Otherwise healthy male or nonpregnant female outpatients aged 18 years or older who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR)[33] criteria for bipolar I disorder (most recent episode: manic or mixed) based on medical records were eligible for the study if they met the following criteria: one or more prior manic or mixed episode; Young Mania Rating Scale (YMRS)[34] score of 16 or more; and currently receiving treatment with an antipsychotic (e.g., olanzapine, risperidone, quetiapine, or aripiprazole) as either monotherapy or in combination with a mood stabilizer (e.g., lithium, valproate, or lamotrigine), and currently changing medication to improve efficacy or side-effect profile. Female subjects had agreed to adhere with acceptable forms of contraception throughout the study.

Subjects who had a history of a lack of therapeutic response to an adequate trial with carbamazepine for the treatment of bipolar I disorder; who met DSM-IV-TR criteria for ultra-rapid cycling (i.e., >6 mood episodes per year);[33] who were judged by the investigator to be acutely at risk for suicidal or violent behavior; or who had histories of serious suicide attempts requiring medical

intervention were excluded from study participation. Additional exclusion criteria included histories of or presence of clinically significant hepatic or renal disease or any other disease that could affect the action, absorption, or disposition of the study drug or assessments; bone marrow depression; seizure disorder (other than a single childhood febrile seizure); myocardial infarction within six months of screening; borderline or antisocial personality disorder or any nonaffective psychotic disorder or mental disorder caused by a general medical condition; current hospitalization for the treatment of psychiatric symptoms; the presence of any other primary Axis I disorder not specifically allowed by the protocol; the presence of any condition that could confound interpretation of the study results or that represented an inappropriate risk to the subject; and a history of hypersensitivity or intolerance to CBZ-ERC.

Study periods. The study comprised three study periods—screening, open-label titration, and observation—and a 30-day follow-up. Subject eligibility was determined during the 2- to 10-day prestudy screening period. Baseline safety and efficacy assessments were performed at the beginning of the four-week titration period, and CBZ-ERC treatment was initiated in all subjects. [The starting dose of 200mg/d was followed by 200mg increases every 3 to 4 days—as tolerated and clinically indicated—to a target dose of 800mg/d BID (maximum dose, 1600mg/d) (Table 1). Dosage adjustments were stopped when the subject's optimal dose was achieved, and downward titration was permitted at any time during treatment to improve tolerability or for safety reasons. Mood stabilizers, with the exception of lithium, were discontinued with a slow downward titration while CBZ-ERC was gradually titrated upward. Lithium (when appropriate) and carbamazepine serum levels were obtained at Weeks 1, 2, 4, and 8 or early termination (ET) (final visit), and were monitored throughout the observation period. At each study visit, safety, adherence, and concomitant medication data were collected and the YMRS[34] was administered. Other efficacy rating scales—(Clinical Global Impressions Scale–Bipolar Version [CGI-BP],[35] Hamilton Rating Scale for Depression, 21-item version [HAM-D_{21}],[36] and Montgomery-Åsberg Depression Rating Scale [MADRS])[37]—were administered at baseline (Week 0) and Week 4. Subjects continued their CBZ-ERC optimal dose during the four-week observation period; however, the dosage might have been reduced at any time during the treatment period to improve tolerance. All efficacy rating scales were administered, and safety, adherence, and concomitant medication data were collected at the final visit (Week 8/ET). Follow-up to collect information on new or ongoing AEs was conducted 30 days after the last dose of the study drug was given.

TABLE 1. CBZ-ERC titration schedule

Days	Total Daily Dose	Twice-Daily Dosing	
		AM	PM
1–3	200mg	—	1 x 200mg
4–7	400mg	1 x 200mg	1 x 200mg
8–11	600mg	1 x 200mg	2 x 200mg
12–14	800mg*	2 x 200mg	2 x 200mg
15–18	1000mg	2 x 200mg	3 x 200mg
19–21	1200mg	3 x 200mg	3 x 200mg
22–25	1400mg	3 x 200mg	4 x 200mg
26–28	1600mg	4 x 200mg	4 x 200mg

CBZ-ERC=carbamazepine extended-release capsules

* Maximum recommended study dosage.

Study drug. CBZ-ERC (Equetro™) is a three-bead (immediate-, extended-, and enteric-release) capsule formulation of carbamazepine. In this open-label study, all subjects were in a single treatment group, so no blinding was required. CBZ-ERC 200mg capsules (lot number ODV040203) were used during the titration period, and 200mg and 300mg capsules (lot number ODV040202) were used during the observation period. Study medication was administered BID, with the morning and evening meals.

Concomitant use of lithium was permitted, provided that a stable dose had been maintained for two weeks before screening; other mood stabilizers (valproate and lamotrigine) were discontinued during the titration period. In addition, concomitant use of benzodiazepines for agitation or sleep as well as the following antipsychotics were permitted: olanzapine, risperidone, quetiapine, and aripiprazole. The dosage of concomitant medications was adjusted, if needed, after the optimal dose of CBZ-ERC had been achieved. Concomitant use of antipsychotics other than those listed above, long-acting, injectable antipsychotics, antidepressants, and clozapine was not permitted. Subjects who needed alternative treatments (e.g., electroconvulsive therapy [ECT], mood stabilizers, or antipsychotics that were not present at baseline) were withdrawn from the study.

Evaluation criteria. *Safety assessments.* Safety assessments, the primary study outcome, included the recording of AEs, laboratory parameters, a physical examination, and medication history (including all medications taken during the course of the study and those taken for three months prior to screening), vital signs, and an electrocardiogram

(ECG). In addition, the total number of days on treatment was summarized for the safety population to determine the extent of study drug exposure.

AE information—defined as any unfavorable and unintended sign, symptom, disease, or exacerbation of a pre-existing condition temporally but not necessarily causally associated with the use of the investigational agent—was collected and recorded from the time of signed informed consent and for 30 days after treatment ended. AE intensity (mild, moderate, or severe) was assessed; the outcome (resolved, unresolved, resolving, resolved with sequelae, death, or unknown) was recorded; and the causal relationship between the AE and study drug was categorized. Serious AEs were those that resulted in death; were life-threatening; required inpatient hospitalization or prolongation of existing hospitalizations; resulted in persistent or significant disability or incapacity; or resulted in a congenital abnormality or birth defect. A treatment-emergent AE (TEAE) was defined as an AE that occurred on or after the first day of double-blind dose of study medication; a treatment-related AE was defined as a TEAE considered by the investigator to be causally related to the study drug.

Laboratory assessments—collected under nonfasting conditions—included biochemistry, hematology, urinalysis, urine pregnancy test, thyroid stimulating hormone (TSH), and serum lithium and carbamazepine levels. The following biochemistry parameters were assessed: sodium, potassium, calcium, urea, creatinine, albumin, total protein, lactic dehydrogenase (LDH), aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin, glucose, and cholesterol. Hematology parameters included hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), total and differential white blood cell (WBC) count, and platelet count. Urine was analyzed for glucose, blood, protein, and pH, and a drug screen was performed. Biochemistry, hematology, urinalysis, and TSH samples were obtained at screening, at Week 4, and again at Week 8/ET. The drug screen was performed at screening and Week 8/ET; serum lithium and carbamazepine levels were measured at screening and Weeks 1, 2, 4, and 8/ET. A urine pregnancy test was performed on all females of childbearing potential at screening and Weeks 0, 4, and 8/ET.

A full physical examination was performed at screening and Week 8/ET; height was measured at screening only, and weight was recorded at each study visit. Vital signs—pulse rate and blood pressure (BP)—were measured at each study visit after the subject had been in a sitting position for five minutes. Blood pressure was measured using the same method and the same arm throughout the study. Clinically significant changes from screening in the physical examination and/or vital signs were noted as AEs. A 12-lead ECG was performed with the subject in the supine position; this was read and interpreted by a cardiologist at screening and at Weeks 4 and 8/ET.

Efficacy assessments. The clinician-administered efficacy assessments—administered in this study by qualified raters— included the YMRS,[34] HAM-D_{21},[36] MADRS,[37] and CGI-BP;[35] these are standard measuring instruments used in clinical studies of bipolar disorder. The YMRS, the primary efficacy variable, is an 11-item scale designed to assess the severity of symptoms associated with the manic state of bipolar disorder.[34] Scored on a scale of 0 to 60, with higher scores indicating greater disease severity, the YMRS was administered at screening, baseline, and Weeks 1 through 8/ET. The secondary efficacy variables (HAM-D, MADRS, and CGI-BP) were administered at baseline and Weeks 4 and 8/ET.

The first 17 items of the HAM-D_{21}, a 21-item instrument designed to detect the presence and severity of depression in adults,[36] were included in the score analysis. Four assessed items that were not included in the score analysis are diurnal variation of symptoms, depersonalization and derealization, paranoid symptoms, and obsessional and compulsive symptoms. Scoring of the MADRS,[37] a 10-item instrument designed to detect the presence and severity of depression in adults, was based on a clinical interview. The CGI-BP measures the severity of (CGI-BP-S) and changes in (CGI-BP-C) mania, depression, and overall bipolar illness.[35] The CGI-BP-S measures severity of mania, depression, and overall bipolar illness on a scale ranging from 1 (normal, not ill) to 7 (very severely ill), and the CGI-BP-C evaluates change from the Baseline assessment for each phase of the illness was determined, with grading options ranging from 1 (very much improved) to 7 (very much worse). As with the YMRS, higher scores indicated greater disease severity for all three secondary efficacy assessments.

Statistical methods. All data were summarized using descriptive statistics; no inferential analyses were performed for the safety or efficacy assessments in this study. The number of observations, mean, standard deviation (SD), median, minimum, and maximum values are presented for the numerical variables, and categorical variables are summarized using frequencies and percentages. Calculation of the extent of study drug exposure was determined by converting the number of days of treatment for each subject into weeks, and then summarizing the data continuously as mean number of weeks, and categorically by the number of weeks of drug exposure.

Patients were evaluated based on the safety and intention-to-treat (ITT) populations. The safety population comprised all patients who received one or more doses of the study drug, and served as the basis for the safety evaluation; the ITT population comprised all enrolled patients who received one or more

doses of study drug, had a baseline YMRS evaluation, and one or more postbaseline YMRS evaluations, and served as the basis for the efficacy evaluation.

RESULTS

This study was conducted at 11 sites in the United States between March 8 and October 19, 2005.

Subject disposition. Among the 53 subjects enrolled, 35 (66%) completed the trial and 18 (34%) terminated early (Table 2). The most common reasons for early termination were lost to follow-up (7 subjects [13.2%]) and the occurrence of an AE (9 subjects [17.0%]); one subject withdrew due to lack of efficacy. In addition, one subject who reported a serious AE (abdominal pain) withdrew from the study; however, because the subject did not return to the site for end-of-study procedures, the investigator considered "lost to follow-up" the most appropriate reason for study termination. The safety population comprised 53 (100%) enrolled subjects, and the ITT comprised 52 (98.1%) subjects; one subject was excluded from the ITT population because no postbaseline YMRS data were available.

Subject demographics. The majority of subjects in the safety population were female (64.2%) and white (58.5%), and the mean age was 38.8 years. The subjects' mean weight, 194.7 lbs, was high in both groups, and there were no notable demographic differences between the safety and ITT populations. Mean baseline disease characteristics are summarized in Table 3. The most recent bipolar episode reported was a mixed episode in the majority of subjects (62.3%), and 45.3 percent reported more than 10 previous manic/mixed episodes. All concomitant psychiatric conditions reported at screening were categorized as "history and not active."

Previous medications reported by greater than 10 percent of subjects included antidepressants (96.2%), antiepileptics (28.3%), antihistamines for systemic use (11.3%), and sex hormones and genital modulators (11.3%). All subjects were receiving concomitant antipsychotic medications during the study, including olanzapine (11.3%), risperidone (13.2%), quetiapine (50.9%), and aripiprazole (28.3%). In addition, 24.5 percent were receiving concomitant mood stabilizers, including lithium (7.5%), valproate (15.1%), and lamotrigine (1.9%).

TABLE 2. Summary of subject disposition

	Total, n (%)
ENROLLED POPULATION, N	53
Safety population	53 (100.0)
ITT population	52 (98.1)
Completed study	35 (66.0)
Terminated early	18 (34.0)
REASON FOR TERMINATION	
Lost to follow-up	7 (13.2)
AEs/serious AEs	9 (17.0)
Subject withdrew consent	1 (1.9)
Lack of efficacy	1 (1.9)
REASON NOT IN ITT POPULATION	
No postbaseline assessment	1 (1.9)

AE = adverse event; ITT = intention-to-treat.

Safety evaluations. *Drug exposure.* The total number of days on treatment was summarized for all subjects included in the safety population. The number of days for each subject was converted into weeks, and the data were summarized continuously as mean number of weeks, and categorically by the number of weeks exposed. The aggregate number of patient years on drug was then computed across all subjects. Overall patient exposure to CBZ-ERC was 6.3 patient years, with subjects receiving concomitant antipsychotic medications exposed for 5.8 patient years, and those receiving both antipsychotics and lithium exposed for 0.6 patient years. Mean study drug exposure was slightly longer for subjects who received antipsychotics with lithium (7.54 weeks) compared with those who received concomitant antipsychotics without lithium (6.27 weeks). A majority of the subjects in the overall safety population (63.5%) and in the antipsychotic group (62.5%) were exposed to CBZ-ERC for seven or more weeks; among four subjects in the antipsychotic plus lithium group, three were exposed to CBZ-ERC for more than eight weeks, and one was exposed between two and three weeks. The most common CBZ-ERC dosages administered during the study were 400mg (46 subjects; mean exposure duration 1.95 weeks) and 800mg (42 subjects; mean exposure duration 3.02 weeks). The mean CBZ-ERC daily dose was 696.3mg overall—694.0mg in the antipsychotic group and 723.9mg in the antipsychotic plus lithium group.

Adverse events. Treatment-emergent adverse events (TEAEs) were summarized for the overall safety population, and for subsets of subjects receiving the following concomitant medications: antipsychotics (n=49), antipsychotics

TABLE 3. Summary of baseline demographic and disease severity characteristics (safety population)

CHARACTERISTIC	TOTAL N=53
Age (years)	
Mean (SD)	38.8 (10.39)
Gender, n (%)	
Male	19 (35.8)
Female	34 (64.2)
Race, n (%)	
White	31 (58.5)
Black or African-American	12 (22.6)
Hispanic	10 (18.9)
Weight (lbs)	
Mean (SD)	194.7 (54.19)
Height (in)	
Mean (SD)	67.7 (4.08)
Current Bipolar Disorder Diagnosis, n (%)	
Mixed	33 (62.3)
Manic	20 (37.7)
YMRS Total Score	
Mean (SD)	19.5 (4.81)
HAM-D Total Score	
Mean (SD)	11.1 (6.79)
MADRS Total Score	
Mean (SD)	14.5 (8.83)
CGI-BP-Severity (Overall), n (%)	
Normal, not ill	0
Minimally ill	0
Mildly ill	12 (22.6)
Moderately ill	34 (64.2)
Markedly ill	7 (13.2)
Severely ill	0
Very severely ill	0
CGI-BP-Severity (Mania), n (%)	
Normal, not ill	0
Minimally ill	1 (1.9)
Mildly ill	13 (24.5)
Moderately ill	36 (67.9)
Markedly ill	3 (5.7)
Severely ill	0
Very severely ill	0
CGI-BP-Severity (Depression), n (%)	
Normal, not ill	16 (30.2)
Minimally ill	7 (13.2)
Mildly ill	11 (20.8)
Moderately ill	15 (28.3)
Markedly ill	4 (7.5)
Severely ill	0
Very severely ill	0

BID=twice daily; CGI-BP=Clinical Global Impressions Scale–Bipolar Version; HAM-D=Hamilton Rating Scale for Depression; in=inches; lbs=pounds; MADRS=Montgomery-Åsberg Depression Rating Scale; QHS=once daily at bedtime; SD=standard deviation; YMRS=Young Mania Rating Scale

with lithium (n=4), olanzapine (n=6), risperidone (n=7), quetiapine (n=27), and aripiprazole (n=15). Subjects receiving antipsychotics plus lithium (4) were excluded from the data summaries of those receiving concomitant antipsychotics because the numbers were insufficient for a meaningful analysis.

In the overall safety population, 84.9 percent of subjects reported TEAEs during the study (Table 4). The most commonly reported TEAEs (≥10% of subjects in the safety population) were somnolence (26.4%), sedation (22.6%), dizziness (20.8%), headache (17.0%), and nausea (13.2%). Weight gain was reported as an AE for three subjects (5.7%), with the maximum weight increases from screening ranging from 7.1 to 12.2 percent. The subject with the greatest increase in weight withdrew from the study because of an AE of weight gain; this subject was receiving concomitant valproate and quetiapine.

AEs were reported by 83.7 percent of subjects who received concomitant antipsychotics and by 100 percent of subjects receiving concomitant antipsychotics plus lithium. The distribution of the most commonly reported TEAEs among subjects receiving concomitant antipsychotics was similar to that of the overall safety population; however, it differed among those who were on concomitant antipsychotics plus lithium. None of the subjects in this group reported dizziness or sedation, which were among the most commonly reported AEs in subjects in the overall safety population; however, it was not possible to assess the importance of this finding due to the small number of subjects in this subgroup. Further, AEs differed among subjects receiving different antipsychotics. All subjects receiving concomitant olanzapine (n=6) or risperidone (n=7) reported AEs; 81.5 percent receiving quetiapine (n=27) and 80 percent receiving aripiprazole (n=15) reported AEs. The most commonly reported TEAEs in the safety population (somnolence, sedation, dizziness, headache, and

nausea) were also reported in subjects receiving antipsychotics, with the exception of nausea, dizziness, and headache, which were not reported in subjects receiving olanzapine.

Most AEs were mild or moderate in severity, with eight subjects (15.1%) experiencing severe AEs. Overall, 31 (58.5%) TEAEs were rated as mild and 24 (45.3%) as moderate. With the exception of the 15 subjects who received concomitant aripiprazole, more than 50 percent of TEAEs in subjects receiving antipsychotics and/or lithium were rated as mild in intensity. Among subjects receiving aripiprazole, 10 (31.3%) of the TEAEs were rated as mild, 18 (56.3%) moderate, and four (12.5%) severe. No severe TEAE was reported by more than one subject. The distribution of severe TEAEs among subjects in the antipsychotic subgroups was as follows: lithium (0); olanzapine (0); aripiprazole (thrombocytopenia, diarrhea, asthenia, and sedation); quetiapine (nausea, influenza-like illness, priapism); and risperidone (dizziness). AEs leading to study discontinuation were reported in 10 subjects. Among the AEs leading to study discontinuation, only rash and sedation were reported by more than one subject and were considered to be study-drug related. Serious AEs were reported by three subjects: one subject withdrew from the study due to abdominal pain that was considered unrelated to the study drug; one subject reported priapism that was considered possibly related to the study drug; and one subject was hospitalized for increased bipolar symptoms that had begun during screening, so the subject was not administered the study drug. No deaths were reported during the study.

Laboratory evaluations. Laboratory evaluations, vital signs, and ECG data were summarized for the overall safety population, and for subsets of subjects who received antipsychotics alone or combined with lithium. Overall, mean changes in hematology parameters from screening to Week 8/ET were small, with values reported within the normal range for the majority of subjects. Greater than 10 percent of subjects had abnormal WBC counts at Week 8/ET; three subjects had abnormally low WBC counts and two had abnormally high WBC counts. The mean change in WBC count from screening to Week 8/ET was -0.646x10^3/µL. Most subjects with abnormal hematology results at Week 8/ET were from the subgroup receiving antipsychotic medications. Among those receiving antipsychotics plus lithium, one had a decreased RBC count and one had abnormal hemoglobin. Clinically significant

TABLE 4. Treatment-emergent adverse events* reported by ≥5% of subjects

SYSTEM ORGAN CLASS (MedDRA Version 7.0)	SAFETY POPULATION	ANTIPSYCHOTICS§	ANTIPSYCHOTICS with Lithium
Adverse Event	*n*=53	*n*=49	*n*=4
(Preferred Term)	*n* (%)	*n* (%)	*n* (%)
Any Adverse Event	**45 (84.9)**	**41 (83.7)**	**4 (100.0)**
Gastrointestinal Disorders	**20 (37.7)**	**17 (34.7)**	**3 (75.0)**
Abdominal pain	3 (5.7)	2 (4.1)	1 (25.0)
Constipation	3 (5.7)	2 (4.1)	1 (25.0)
Diarrhea	5 (9.4)	5 (10.2)	0
Dry mouth	4 (7.5)	3 (6.1)	1 (25.0)
Nausea	7 (13.2)	6 (12.2)	1 (25.0)
General Disorders/ Administration Site Conditions	**10 (18.9)**	**9 (18.4)**	**1 (25.0)**
Asthenia	3 (5.7)	3 (6.1)	0
Investigations	**6 (11.3)**	**6 (12.2)**	**0**
Weight increased	3 (5.7)	3 (6.1)	0
Nervous System Disorders	**36 (67.9)**	**33 (67.3)**	**3 (75.0)**
Dizziness	11 (20.8)	11 (22.4)	0
Headache	9 (17.0)	7 (14.3)	2 (50.0)
Sedation	12 (22.6)	12 (24.5)	0
Somnolence	14 (26.4)	12 (24.5)	2 (50.0)
Psychiatric disorders	**7 (13.2)**	**6 (12.2)**	**1 (25.0)**
Insomnia	4 (7.5)	3 (6.1)	1 (25.0)
Skin and Subcutaneous Tissue Disorders	**11 (20.8)**	**10 (20.4)**	**1 (25.0)**
Rash	3 (5.7)	3 (6.1)	0

*An AE was considered treatment-emergent if it began on or after the dates of the first dose of study drug or if there was an increase in intensity of a pre-existing condition.

§Summaries for subjects who received antipsychotics do not include subjects who also received lithium.

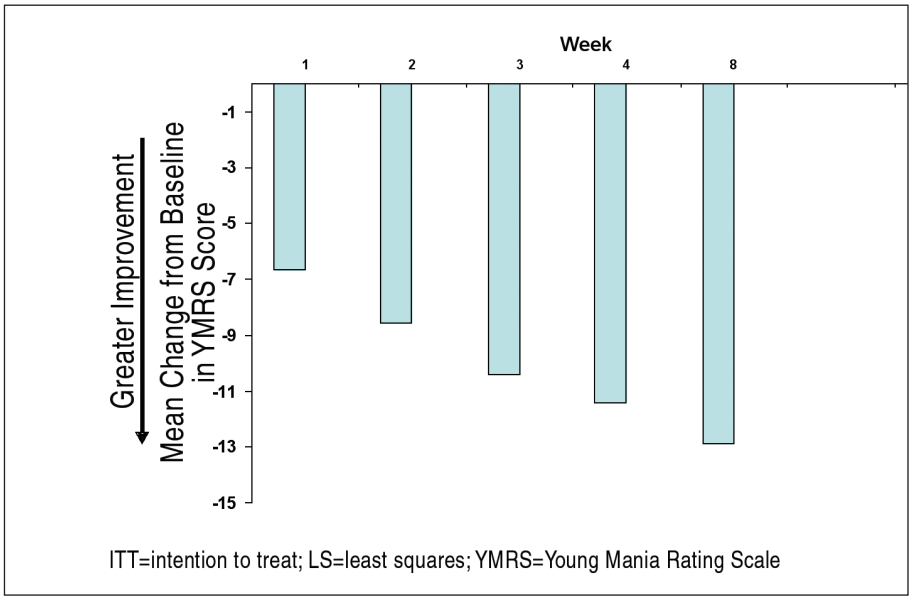

FIGURE 1. Mean change from baseline in Young Mania Rating Scale (ITT population)

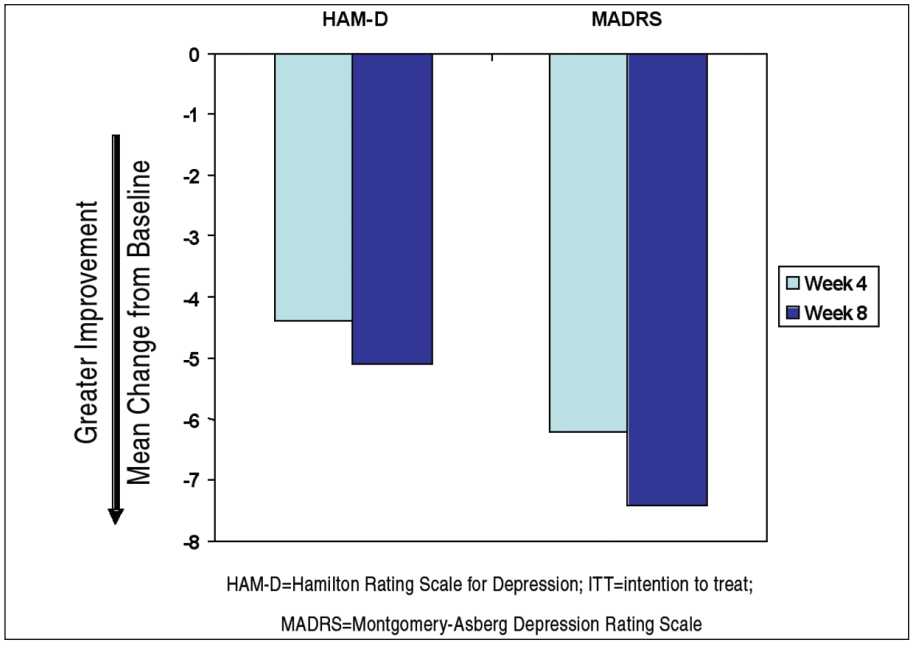

FIGURE 2. Mean change from baseline in HAM-D and MADRS (ITT population)

abnormalities were reported for four subjects, as follows: one low neutrophil ($1.15x10^3$/µL) and WBC ($2.4x10^3$/µL) counts; one low neutrophil ($1.11x10^3$/µL) and WBC ($2.7x10^3$/µL) counts with elevated lymphocytes ($1.72x10^3$/µL); one low WBC ($2.9x10^3$/µL) count; and one elevated lymphocyte ($6.21x10^3$/µL) count. Among these four subjects, three had abnormal values at screening. Two (2) subjects discontinued the study drug because of hematologic abnormalities (thrombocytopenia [1]; decreased neutrophil count [1]).

Despite the fact that fasting was not required for clinical chemistry samples, mean changes in chemistry and electrolyte values from screening to Week 8/ET were small in most subjects. However, more than 10 percent of subjects with laboratory data at Week 8/ET had abnormally high results for the following parameters: GGT (n=15, mean increase 33.514U/L); cholesterol (n=7, mean increase 16.595mg/dL); glucose (n=5, mean increase 8.757mg/dL); ALT (n=5, mean increase 0.649U/L); AST (n=4, mean increase 1.351U/L); ALP (n=4, mean increase 8.4U/L); and TSH (n=4, mean increase 0.4µIU/mL). Most subjects with abnormal serum chemistry results at Week 8/ET were from the subgroup that received antipsychotics, and most of them received quetiapine (the most commonly prescribed antipsychotic in this study). Abnormalities in clinical chemistry results in subjects receiving antipsychotics plus lithium included elevated glucose, decreased glucose, and elevated GGT (1 subject each).

A total of 33 subjects had serum CBZ levels outside of the normal range during at least one study time point. Approximately half of the abnormal values occurred during the first or second week of the study, and in most cases these values were abnormally low during the study medication titration period. Clinically significant serum chemistry/electrolyte abnormalities were reported in 15 subjects after the first dose of study drug; among these subjects, 10 were receiving concomitant quetiapine. The most common clinically significant abnormality in chemistry parameters was TSH (n=7); six of these subjects received concomitant quetiapine and two had abnormal results at screening. Although clinically significant GGT abnormalities were reported in four subjects, no other liver function test parameters were clinically significant in any subjects. Among the four subjects with clinically significant elevated glucose, three had a medical history of type 2 diabetes. One (1) subject discontinued the study drug because of hyponatremia (122mmol/L). Concomitant medications other than quetiapine taken by subjects who developed clinically significant serum chemistry abnormalities included olanzapine (increased potassium [1 subject] and increased GGT [1 subject]); aripiprazole (increased glucose [1 subject]); aripiprazole and

lithium (increased glucose [1 subject]); and olanzapine and aripiprazole (increased GGT and TSH [1 subject]).

Clinically significant abnormal urinalysis results included elevated urine glucose (n=3) and blood in the urine (n=1). All three subjects with abnormal urine glucose had type 2 diabetes at screening, and the subject with blood in the urine was female, suggesting menstrual blood contamination. Serum carbamazepine values outside therapeutic range (4.0–10µg/mL) were reported at least once during the study in 33/53 (62.3%) of subjects. Most of these were abnormally low levels, and approximately half occurred during the first two weeks of the study. Among the four subjects receiving concomitant lithium, three maintained therapeutic serum carbamazepine levels (0.6–1.2mEq/L) throughout the study, while one had consistently low levels.

Few changes relative to screening were reported for other safety parameters. On the physical examination, changes in rash were reported in two subjects and skin redness was reported in one; other skin changes included superficial ulcerations of both feet in one subject. No clinically significant mean changes from baseline were observed in vital signs (pulse rate, blood pressure, temperature, and weight) at Week 8/ET. The mean change in weight in the overall safety population was 1.2 lbs; in the subgroup receiving concomitant antipsychotics it was 1.1 lbs, and in the subgroup receiving antipsychotics plus lithium it was 1.5 lbs. At screening, 64.2 percent of subjects had normal ECGs, and none of the remaining 35.8 percent had clinically significant abnormalities. One subject in the antipsychotic plus lithium subgroup had an abnormal and clinically significant ECG at Week 4. At the end of the study, 49.1 percent of subjects had normal ECGs, and there were no clinically significant abnormal findings.

Efficacy results. There was a mean decrease in the total YMRS score from baseline at each study visit, indicating improvement in the severity of manic symptoms. As illustrated in Figure 1, the mean decrease from baseline was progressively greater at each postbaseline visit, with the mean (SD) decrease -6.7 (6.13) points at Week 1 and -12.9 (6.43) points at Week 8/ET.

There also was a mean decrease from baseline at Weeks 4 and 8/ET in the secondary efficacy variables, HAM-D and MADRS, indicating improvement in the severity of depression (Figure 2). The mean (SD) HAM-D score at baseline was 11.2 (6.84), and the mean decrease from baseline at Week 4 was -4.4 (6.11) and at Week 8/ET -5.1 (6.39). Similarly, the mean (SD) MADRS score at baseline was 14.5 (8.92). and the mean decrease from baseline was -6.2 (8.77) at Week 4 and -7.4 (7.97) at Week 8/ET.

Each of the three CGI-BP components—mania, depression, and overall bipolar disorder—improved during the study, demonstrating reduced severity of bipolar illness. For overall bipolar disorder, the percentage of subjects rated as "moderately ill" or "markedly ill" at baseline (n=40, 77.0%) on the CGI-BP-S decreased at Week 4 (n=10, 21.7%) and at Week 8/ET (n=7, 17.9%). Further, the percentage rated as "improved" ("very much improved" or "much improved") on the CGI-BP-C increased over time (Week 4, n=24 [52.2%]; Week 8/ET, n=23 [60.5%]), while the percentage rated as "not improved" ("minimally improved," "no change," "minimally worse," "much worse," and "very much worse") decreased over time (Week 4, n=22 [47.8%]; Week 8/ET, n=15 [39.5%]). Similar findings were reported for the mania and depression components of the CGI-BP. For the mania component, the percentage rated "moderately ill" or "markedly ill"on the CGI-BP-S at baseline (n=38, 73.1%) decreased at Week 4 (n=5, 10.9%) and at Week 8/ET (n=5, 12.8%), the percentage rated as "improved" on the CGI-BP-C increased over time (Week 4, n=27 [58.7%]; Week 8/ET, n=23 [60.5%]), and the percentage rated as "not improved" on the CGI-BP-C decreased over time (Week 4, n=19 [41.4%]; Week 8/ET, n=15 [39.5%]). For the depression component, the percentage of subjects rated as "moderately ill" or "markedly ill" on the CGI-BP-S at baseline (n=19,

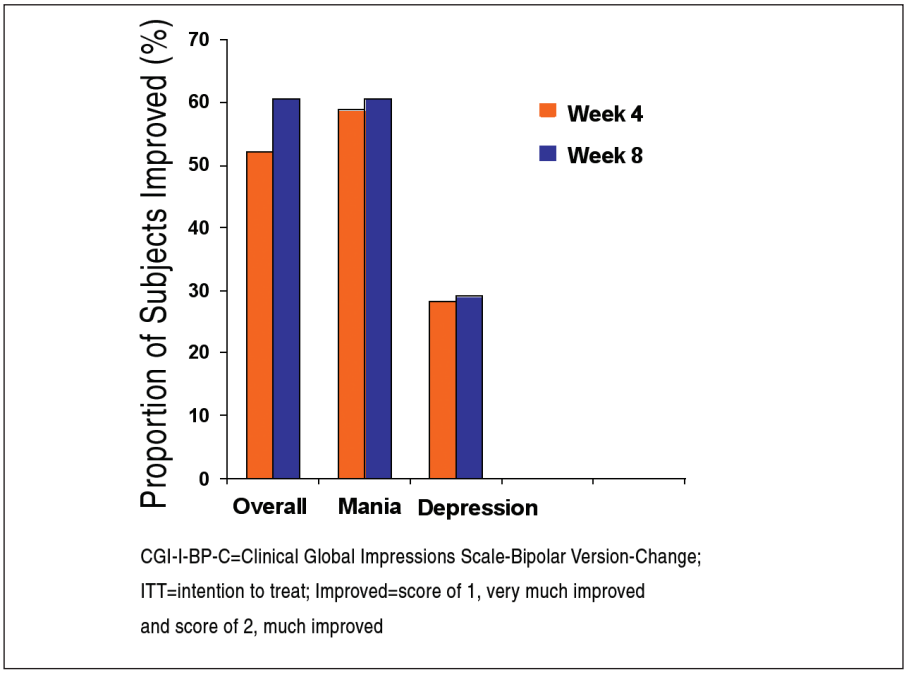

FIGURE 3. Percentage of subjects with improvement on each component of the CGI-BP-C (ITT population)

36.5%) decreased at Week 4 (n=9, 19.6%) and at Week 8/ET (n=7, 17.9%), the percentage rated as "improved" on the CGI-BP-C increased over time (Week 4, n=13 [28.3%]; Week 8/ET, n=11 [29.0%]), and the percentage rated as "not improved" on the CGI-BP-C decreased over time (Week 4, n=33 [71.7%]; Week 8/ET, n=27 [71.0%]). Figure 3 summarizes the percentage of improvement at Week 4 and Week 8/ET on the three components of the CGI-BP-C.

DISCUSSION

Based on current trends in the management of bipolar disorder,[18,24,25] it is anticipated that CBZ-ERC will be used as combination therapy, and subjects were, therefore, allowed to continue on lithium and/or antipsychotics (e.g., olanzapine, risperidone, quetiapine, and aripiprazole) in the present study to evaluate CBZ-ERC in a "real-world" setting. Results showed the agent to be safe and generally well tolerated when administered as combination therapy, with the majority of TEAEs rated as mild or moderate in severity, and only eight (15.1%) subjects experiencing AEs rated as severe. The most commonly reported TEAEs (≥10%) were somnolence, sedation, dizziness, headache, and nausea; these were also the most commonly reported AEs in previously published clinical trials with CBZ-ERC as monotherapy for the acute treatment of bipolar disorder in an inpatient setting in which a more aggressive dose titration strategy was used.[4,5] All reports of severe TEAEs were in the subjects in the subgroup treated with concomitant antipsychotics; however, none of these were in the subjects who had received olanzapine or lithium. Ten subjects discontinued the study drug because of AEs; rash and sedation—commonly occurring AEs with CBZ—were the only events leading to study discontinuation in more than one subject. In general, changes in laboratory test results were small and not clinically significant, and there were no notable changes in the other safety assessments (e.g., physical examination, vital signs, and ECG), although one subject on concomitant valproate and quetiapine withdrew from the study because of weight gain. The mean reduction from baseline in the YMRS score was -6.7 points after one week and -12.9 points after eight weeks, indicating improvement in the severity of mania. HAM-D and MADRS total scores also showed mean reductions, indicating patient improvement in depressive symptoms as well, and all three components of the CGI-BP-S and CGI-BP-C improved during the study, indicating overall improvement in the symptoms of bipolar disorder.

Carbamazepine has been widely used for many years in psychiatric and neurologic settings, and its AE profile is well-defined.[16] An early study of CBZ in bipolar disorder reported AEs consistent with those observed when it was used for treatment of other conditions (>10% experienced dizziness, ataxia, clumsiness, drowsiness, slurred speech, diplopia).[38] Recent studies with the FDA-approved, extended-release formulation (CBZ-ERC) have supported its general tolerability in patients with bipolar disorder.[4,5]

The high rates of overweight and obesity that have been reported in patients with bipolar disorder are problematic[39,40] and are considered sufficiently bothersome by patients and physicians to interfere with medication adherence.[41,42] In addition, it has been shown that some FDA-approved agents for bipolar disorder—especially atypical antipsychotics—are associated with metabolic effects (e.g., weight gain, diabetes, hyperlipidemia),[43] which may contribute to an already high rate of metabolic syndrome among patients with bipolar disorder.[44] Among the atypical antipsychotics permitted in this study, weight gain was most common with olanzapine, followed by risperidone and quetiapine;[43,45] aripiprazole is associated with only negligible weight gain.[46] Among the mood stabilizers, weight gain is most often seen with valproic acid, followed by lithium; CBZ has not been associated with clinically significant weight gain.[4,5,45] Although total cholesterol levels increased from baseline in subjects on concomitant atypical antipsychotic agents in this study, the implications of this trend with regard to development of metabolic syndrome is unknown, as other lipids were not measured and the use of concomitant agents confound the results. Metabolic syndrome is therefore not considered a significant issue with CBZ-ERC monotherapy,[47] and combination treatment with anticonvulsants and lithium has been reported to have the most favorable AE profile.[26]

This study was designed with a gradual four-week titration period, beginning with a low CBZ-ERC dose of 200mg/d, which represents half the starting dose used in the acute inpatient trials.[4,5] Beginning treatment with a modest dose, followed by gradual upward titration (200mg every 3 to 4 days, as tolerated), has been suggested by other investigators as one way to improve the tolerability of combination regimens used in the treatment of bipolar disorder.[26] As anticipated, CBZ-ERC tolerability showed a trend toward improvement compared with that in previous clinical trials with monotherapy, with the overall incidence of TEAEs (84.9%) lower compared with approximately 90 percent reported with a more rapid (7-day) titration period.[4,5,48] In addition, in a pooled analysis of two inpatient trials, AEs occurred most frequently during dose titration, with their incidence markedly decreasing over the three-week study duration, lending further support to the theory that the improvement in the incidence of AEs in this study can be explained by the longer, more gradual titration period.[48]

This study had several limitations. First, it is difficult to assess the clinical impact of safety data specific to CBZ-ERC in patients who are receiving concomitant therapy; however, because the data in this study demonstrated an AE profile that was, for the most part, similar to that of previous trials with CBZ-ERC

monotherapy, it was concluded that CBZ-ERC is generally well tolerated in combination therapy. Although no overall safety trends were seen with concomitant therapies, the small numbers in the risperidone, olanzapine, and lithium subgroups make it difficult to assess the impact of concomitant therapy with these two agents. Another limitation in the interpretation of the safety results is that blood was collected in the nonfasting state, so clinical chemistry values must be viewed accordingly. Finally, interpretation of the efficacy results in this study is limited by the lack of a randomized, double-blind, placebo-controlled study design. These limitations signal the need for a more systematic evaluation of specific combination therapies compared with monotherapy in the management of bipolar disorder.[12]

CONCLUSIONS

The results of this study generally support the safety and efficacy of CBZ-ERC for patients with bipolar disorder who require combination therapy. CBZ-ERC was safe and generally well tolerated by patients with bipolar I disorder when it was administered concomitantly with other mood stabilizers and atypical antipsychotic medications. Its safety profile appears to be comparable to previous safety profiles for CBZ, with the most frequently reported TEAEs similar to those most often reported in previous studies of CBZ-ERC in patients with bipolar disorder, and these findings suggest a trend toward improved tolerability compared with studies that used faster titration rates. Changes in laboratory test results were generally small, not clinically significant, and comparable to those that had been reported in previous CBZ-ERC trials. Improvements in the efficacy assessments—also consistent with those of other studies—indicated improvement in symptoms of bipolar disorder with CBZ-ERC administered BID. Further study of CBZ-ERC as a component of a combination regimen in a larger population of patients with bipolar disorder is needed to confirm these findings.

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